



## Clinical trial results: The effect of melatonin on nocturnal enuresis Summary

EudraCT number	2011-004138-33
Trial protocol	DK
Global end of trial date	06 May 2019

### Results information

Result version number	v1 (current)
This version publication date	13 May 2021
First version publication date	13 May 2021
Summary attachment (see zip file)	Supplementary info EudraCT 2011-004138-33 (Supplementary info EudraCT 2011-004138-33.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	EnuMel-11
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01575678
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul Jensen Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Britt Borg, Aarhus University Hospital, 0045 22740973, bborg@clin.au.dk
Scientific contact	Britt Borg, Aarhus University Hospital, 0045 22740973, bborg@clin.au.dk

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	12 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2019
Global end of trial reached?	Yes
Global end of trial date	06 May 2019
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

To investigate the effect of melatonin in fixed dosage before bedtime in children with monosymptomatic nocturnal enuresis on the number of wet nights per week compared with placebo.

Protection of trial subjects:

Blood- and urinesamples obtained at every follow up to monitor adverse events

Background therapy:

none

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	16
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

All subject recruited from the outpatient clinic Center for Child Incontinence, Pediatric Department, Aarhus University Hospital

### Pre-assignment

Screening details:

Patients from Centre for Child Incontinence was screened bases on their previous hospital records. If records were in accordance with inclusion and exclusion criteria, the patient was screened in person by investigators.

Number of screenet patients: 69

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

active and placebo tablets were encapsulated in in grey DB Caps(R) size B

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Melatonin (Circadin, Neurim 2mg)

Arm description:

Subjects receives treatment with Melatonin (Circadin, Neurim 2mg) every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially

Arm type	Experimental
Investigational medicinal product name	Circadin
Investigational medicinal product code	N05CH01o
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

2 mg once every evening for four weeks

<b>Arm title</b>	Placebo
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Arm description:

Subjects received treatment with placebo every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One tablet once every evening for four weeks

<b>Number of subjects in period 1</b>	Melatonin (Circadin, Neurim 2mg)	Placebo
Started	20	20
Completed	18	18
Not completed	2	2
Consent withdrawn by subject	2	2

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Correction: n=20	

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	16	16	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	9.70		
standard deviation	± 1.69	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	17	17	
Previous desmopressin treatment			
Units: Subjects			
Yes	18	18	
No	2	2	
Previous alarm treatment			
Units: Subjects			
Yes	10	10	
No	10	10	
Weight			
Units: kilogram(s)			
arithmetic mean	40.20		
standard deviation	± 10.03	-	
Height			
Units: centimeter			
arithmetic mean	146.65		
standard deviation	± 11.88	-	
Percentage of nights with enuresis			
Units: percent			
arithmetic mean	88.57		

standard deviation	± 15.96	-	
Nocturnal urine production/expected bladder capacity			
Units: percent			
arithmetic mean	124.49		
standard deviation	± 54.16	-	
Maximal voided volume/Expected bladder capacity			
Units: percent			
arithmetic mean	74.70		
standard deviation	± 26.49	-	

## End points

### End points reporting groups

Reporting group title	Melatonin (Circadin, Neurim 2mg)
Reporting group description: Subjects receives treatment with Melatonin (Circadin, Neurim 2mg) every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially	
Reporting group title	Placebo
Reporting group description: Subjects received treatment with placebo every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially.	

### Primary: frequency of nights with enuresis

End point title	frequency of nights with enuresis
End point description:	
End point type	Primary
End point timeframe: registered for each night during the course of four weeks allocated treatment , and the same procedure after cross over to the other treatment allocation	

End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	81.39 (± 25.68)	80.82 (± 26.46)		

### Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Melatonin (Circadin, Neurim 2mg) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.14
upper limit	6.29
Variability estimate	Standard deviation
Dispersion value	11.49

## Secondary: Nocturnal urine production on enuretic nights

End point title	Nocturnal urine production on enuretic nights
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End point description:

End point type	Secondary
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End point timeframe:

registered for each night during the last week of allocated treatment , and the same procedure after cross over to the other treatment allocation

End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: millilitre(s)				
arithmetic mean (standard deviation)	356 (± 109)	355 (± 106)		

## Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Melatonin (Circadin, Neurim 2mg) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.78
upper limit	30.4
Variability estimate	Standard deviation
Dispersion value	55.52



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**Secondary: Adherence to treatment**

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End point title	Adherence to treatment
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End point description:

End point type	Secondary
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End point timeframe:

Same as for the primary endpoint of enuresis frequency:  
(registered for each night during the course of four weeks allocated treatment , and the same procedure after cross over to the other treatment allocation)

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End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: percent				
arithmetic mean (standard deviation)	97.0 (± 4.4)	96.9 (± 3.3)		

**Statistical analyses**

<b>Statistical analysis title</b>	paired t-test
Comparison groups	Melatonin (Circadin, Neurim 2mg) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	2.4
Variability estimate	Standard deviation
Dispersion value	4.6

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**Secondary: Maximal voided volume (MVV)**

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End point title	Maximal voided volume (MVV)
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End point description:

End point type	Secondary
End point timeframe:	
registered each urine output for two days during the last week of allocated treatment, the largest was considered as the MVV(excluding first morning void). The same procedure after cross over to the other treatment allocation	

End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: millilitre(s)				
arithmetic mean (standard deviation)	219.8 (± 105.8)	235.7 (± 95.8)		

### Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Placebo v Melatonin (Circadin, Neurim 2mg)
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-15.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.1
upper limit	25.3
Variability estimate	Standard deviation
Dispersion value	71.4

### Secondary: Daytime fluid intake

End point title	Daytime fluid intake
End point description:	
End point type	Secondary
End point timeframe:	
Same period as for secondary endpoint MVV	

End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: millilitre(s)				
arithmetic mean (standard deviation)	1100 (± 545)	1216 (± 411)		

### Statistical analyses

<b>Statistical analysis title</b>	paired t-test
Comparison groups	Melatonin (Circadin, Neurim 2mg) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-117
Confidence interval	
level	95 %
sides	2-sided
lower limit	-315
upper limit	81
Variability estimate	Standard deviation
Dispersion value	344

### Secondary: Daytime urine output

End point title	Daytime urine output
End point description:	
End point type	Secondary
End point timeframe:	
Same period as for secondary endpoint MVV	

End point values	Melatonin (Circadin, Neurim 2mg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: millilitre(s)				
arithmetic mean (standard deviation)	804 (± 531)	876 (± 362)		

### Statistical analyses

<b>Statistical analysis title</b>	paired t-test
Comparison groups	Melatonin (Circadin, Neurim 2mg) v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-288
upper limit	144
Variability estimate	Standard deviation
Dispersion value	302

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Systematically during the trial after each treatment period.

No systematic registration after trial participation.

Assessment type	Systematic
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### Dictionary used

Dictionary name	Own basic dictionary
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Dictionary version	1
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### Reporting groups

Reporting group title	Melatonin (Circadin, Neurim 2mg)
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Reporting group description:

Adverse event during treatment with melatonin

Reporting group title	Placebo
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Reporting group description:

Adverse event during treatment with placebo

Serious adverse events	Melatonin (Circadin, Neurim 2mg)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Melatonin (Circadin, Neurim 2mg)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	3 / 18 (16.67%)	
Nervous system disorders			
Headache	Additional description: headache for two days, treated with paracetamol		
subjects affected / exposed	5 / 18 (27.78%)	3 / 18 (16.67%)	
occurrences (all)	0	1	
Tiredness	Additional description: Tiredness during daytime. Tiredness in evening shortly after ingestion of studytreatment not included		
subjects affected / exposed	5 / 18 (27.78%)	3 / 18 (16.67%)	
occurrences (all)	3	1	
Insomnia	Additional description: Harder to fall asleep in the evening for two days		

subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 0	3 / 18 (16.67%) 1	
Gastrointestinal disorders			
Appetite disorder	Additional description: Less appetite for four days		
subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 1	3 / 18 (16.67%) 0	
Constipation	Additional description: mild for two weeks		
subjects affected / exposed occurrences (all)	5 / 18 (27.78%) 1	3 / 18 (16.67%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 October 2014	Lack of resources for personnel to run the trial	02 July 2018

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

-Early termination leads to small number of subjects for statistical analysis.  
-Technical problems with armbands leading to a big amount of missing data for the following endpoints: activity, skin temperature, galvanic skin response. Data not shown

Notes: